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Deactivation DNA Polymerase and Hexokinase Enzymes by Radioisotope ^{28}Mg in Cancer Treatment Research

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ABSTRACT

Cancer cells differ with healthy cells in that they grow very fast, uncontrolled and hardly die. They need a lot of enzymes in quantitative term than healthy cells for their metabolic processes, of which there are two particularly important enzymes: Hexokinase and DNA polymerase. The enzymes are interesting due to the catalyst the energy metabolism and replicate the DNA. They possess the same magnesium metal ion cofactor. The use of beta-decay radioisotopes to replace stable metals in the cofactor enzymes to deactivate them is a new trend for cancer treatment research. In this work, ^{28}Mg is used to replace a stable Mg in the enzymes. Deactivated hexokinase may stop or disturb the supply of energy in tumor cells. Deactivated DNA polymerase may stop or disturb DNA replication. Disturbing these two important processes, tumors can stop development and even be destroyed. Besides, during deactivating radioactive isotopes will bombard tumor cells on the spot with a nearly 100% chance of hitting.

Keywords: ^{28}Mg, Deactivation, Hexokinase, DNA polymerase

INTRODUCTION

Chemotherapy and radiotherapy are the two most commonly used methods in cancer treatment nowadays. There are many natural and artificial substances used to influence different metabolic stages in tumor cells. The use of different inhibitors occupied of active site can inactivate the enzymes [1-6], chemicals combined with gene technology to influence to the process of recognizing T cell's enemies in the immune system [7] or using natural complexes to enhance the effective results for chemotherapy and radiation [8]. So far, these methods have been more or less effective but they cannot be said to be highly effective in treating cancer. They also cause significant side effects on patients. Destroying tumor cells is another priority in treatment. Physical agents: heat-laser knife [9], high-frequency oscillation [10] radiation sources and radioactivity [11,12], have also been studied. Powerful radiation devices such as radium needles, Co-60, Cs-137 sources and linear accelerators [11-16] are being used in most oncology centers around the world. Accompanied by radiation sources are beam simulation techniques to focus radiation on the target and to limit the adverse effects of radiation therapy [13]. Nuclear medicine also developed very quickly to meet the process of examination and treatment [14]. Bringing radioactive substances to the target is one of the most successful examples of treating thyroid cancer with ^{131}I isotopes [15]. It can be said that radiotherapy applications have become a huge industry with a lot of investment in scientific research and creating technology lines for manufacturing accelerators and increasingly sophisticated radiation sources and modern. However, the expectations of this approach are still a problem and it cannot be seen as the most effective way of treating cancer, even though it is widely used around the world.

For survive and expand, the cancer cells need more energy than the normal ones. The catalyst for energy supply is the Hexokinase enzyme, a metal cofactor enzyme. There is a divalent magnesium ion at the active site of this enzyme. The Mg ion can react with ATP molecular, an energy unit, through the mitochondrial membrane in the cell to convert to ADP molecular and release the energy [17-20]. This is the first stage of the cell's energy metabolism cycle. If this stage is interrupted, the energy cycle could be manipulated. Cells will starve and may die. Somehow, deactivation Hexokinase, we can disrupt the energy cycle.

DNA replication will make the cancer cells faster multiply and grow. This is the most complex cycle in nature, many

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substrates and enzymes involved in this cycle. For example, helicase to split DNA helix to double strands, then recombine each strand into a new DNA chain by DNA polymerase enzyme family, of which DNA polymerase III plays the most important role. Many studies on the role of DNA polymerase in the formation and development of cancer are carried out. They also anticipate the enzyme's restriction or deactivation in cancer treatment by chemotherapy [21-25].

DNA polymerase is also a cofactor enzyme, in which two metallic elements Magnesium and Zinc located at active site [26,27]. The process of DNA separation and cloning take place at a fork, where all involved elements in this process converge. This location is also the destination or target for the needed agents to inhibit or makes replication errors. Somehow deactivation the DNA polymerase can stop DNA replication. Cancer cells will not replicate or they will replicate errors. The tumor will not grow and gradually shrink by losing the older cells, and the cancer mass is destroyed systematically. In the case of faulty DNA replication, the T cell will recognize and the body's immune system will destroy them.

The assumption that radioisotope ^{28}Mg, somehow, can replace stable magnesium ion in the Hexokinase and DNA polymerase enzyme, these enzymes will be deactivated due to the decays of ^{28}Mg at the active site changed to ^{28}Al and then ^{28}Si. Obviously, just only one radioactive isotope ^{28}Mg can stop or interrupt the two most important metabolic processes, which are the power supply and the DNA replicate of cancer cells. It is a combination of the two most successful traditional cancer treatments, chemotherapy and radiotherapy. The chemotherapy is deactivation the enzymes. Radiotherapy is irradiation the cancer cells on the spot with a probability of reaching nearly 100% by beta particles, X-rays, gamma rays and bremsstrahlung radiations.

MATERIALS AND METHODS

Magnesium is an essential element in human health [28-30]. It plays an important role in metabolism processes. It exists in cofactor enzymes [31-33] including Hexokinase and DNA polymerase. Magnesium can transport into the cell and the different cellular organelles [33]. Many works have carried out and published surrounding Mg problem, both of a deficiency and an excess of Mg nutrition [34-43]. Magnesium has three stable isotopes and some radioisotopes [44]. The organism accepts Mg isotopes in their compounds or substrates without differently seeing due to the similar valence of Mg. Among of radioisotopes of magnesium, only ^{28}Mg can have enough condition for replacing stable Mg in cofactor enzymes [45]. ^{28}Mg is a pure beta decay isotope (100% intensity) with a half time 20.9 h. It emits three electrons 0.211, 0.458 and 0.859 MeV in maximum energy accompanying with fours gamma rays and a lot of X-rays [44]. It has been produced by ^{6}Li + ^{26}Mg alloy + thermal neutron or (27Al, α, 3p) nuclear reactions [46]. Its decayed product is a 28Al isotope. The 28Al is also pure beta decay isotope (100% intensity) with a half time 2.3 min. The isotope emits an electron with 2.87 MeV in maximum energy accompanying with a gamma-ray 1.779 MeV in energy. After decay, ^{28}Al changes to stable ^{28}Si isotope [44].

Hexokinase and DNA polymerase are two used enzymes in this propositional investigation.

Somehow, if the ^{28}Mg is transferred to the tumor cells, the enzymes with Mg cofactor will be deactivated and the tumor cells will be injured.

RESULTS AND DISCUSSION

The average energy of beta particles is used to in internal irradiation. The calculated average energies of beta particles for ^{28}Mg and ^{28}Al are 0.139 MeV and 1.114 MeV, respectively. According to Coderre [47], if the one MBq activity of ^{28}Mg is injected, the calculated absorbed dose rates of ^{28}Mg and ^{28}Al in tumor cells are 0.83 cGy/s and 1.78 cGy/s, respectively. These absorbed doses are below the limited dose for internal irradiation [48]. This activity is equivalent to 1.085E+11 ions or 5.016 E-12 g ^{28}Mg. These number of ions can target to hexokinase and DNA polymerase accordingly competition mechanism. The beta particles calculated maximum ranges of ^{28}Mg and ^{28}Al isotopes in body tissue are 62.19 mg/cm^2 and 143.91 mg/cm^2, respectively [49]. The results are equivalent to about 0,06 cm and 0,14 cm in an effective radius, respectively, if the average tissue density is considered as 0.96 kg/L. These results show that the radioisotopes can interaction with healthyl cells with above interval in the case the isotopes located at the edge of the tumor body. It should take account that is a side effect of this method.

The assumption that somehow the one MBq of the ^{28}Mg pharma product can intravenously inject into the cancer cells. The Hexokinase and DNA polymerase enzymes can obtain ^{28}Mg as the cofactor. The situation is the same ^{131}I competitive with the stable Iodine in the thyroid gland [15].

Bustamante and Pedersen [50] showed the high concentration of hexokinase in tumor cells of rats. The concentration of hexokinase in tumor cells is about 200 times higher than in healthy cells. Due to the tumor cells increasingly need divalent Mg. The supply of ^{28}Mg isotope can carry out to replace the stable Mg. There is no report to the high content of the DNA polymerase in the tumor cells. It should be taking into account that, the DNA replication of tumor cells is more rapidly than healthy cells, especially in metastasis phase. The tumor parasites onto the host organs but they increase in size very fast. By these, they need more substrate, energy, DNA replication and others to survival, development and growing up. They also need more enzymes, in which DNA polymerase is the most important one. Benzekry [51] showed the classical mathematical models for description and prediction of experimental tumor

growth, in which the authors pointed out that the grown rate of tumor cell, is very fast. The tumor cells are highly avidity for Mg, seemly they are Mg traps and the intracellular Mg content is higher than extracellular Mg content [52]. By this reason, the supplying of ^{28}Mg could be targeting to DNA polymerase.

Studies using ^{28}Mg by human intravenous route Silver et al. [53] indicate that the absorption of Mg^{2+} in the gastrointestinal tract is very negligible. Isotope balance with magnesium in the body is slow about 10% to 25% of the whole after 40-60 h and up to 90 h to reach 30% [53]. Nevertheless, the rest of ^{28}Mg amount is about 25%, 12.5% and 6.25%, respectively, due to its decay for the above interval time. The true remained of ^{28}Mg amount of the total injected amount in the above balance periods are 2.5%, 3.12% and 1.87%, respectively. Thus, it noted that after 40 h the most of ^{28}Mg amount is excreted out of the body by urine. This should be considered when carrying out the clinical experiment.

As we have known, the cell needs energy to all its cycle. The energy unite of every organism is an ATP molecular. The ATP is created at mitochondria then is changed to ADP by hexokinase and these process products the energy [54]. The ATP will not be converted to ADP due to hexokinase was deactivation. The cell will be loose the functions due to lack of energy.

In the case of the cell duplication, after DNA is unzipped into two strands, the cell's substrates and structured materials focus onto the fork. The DNA replication takes place by DNA polymerase helping. When the DNA polymerase is deactivation the old cell was dying due to the DNA was separated and cannot recover. The new one cannot generate because the DNA is not replication. Consequently, the tumor mass will be narrow.

Somehow, the ^{28}Mg isotope is transferred to the tumor cells it can compete to the stable Mg at the active site of the hexokinase and the DNA polymerase. Due to the ^{28}Mg decays to the ^{28}Al then to the ^{28}Si in situ. Both of the ^{28}Al and the ^{28}Si are not the cofactor of these enzymes anymore, the consequence is that two enzymes are deactivated.

Deactivation the hexokinase and DNA polymerase is very impacted to growing and duplicating of the tumor cells. It forbids the transferring of ATP to ADP, stops the replication of DNA. When both of process is inhibited the tumor cell would be harmful.

The irradiation due to the decayed ^{28}Mg and ^{28}Al will bombard the tumor cells in situ by beta particles, gamma-rays, X-rays and bremsstrahlung radiations. The probabilities of this bombardment are of about a hundred percent and do not cause significant side effects. This process causes the wounded to the tumor cells.

The free radicals created from radiation effect with intracellular fluid, in turn, will react with substrates and nucleotide molecules. Consequently, these materials will be damaged. The tumor cell will be injured.

Three above processes act into the tumor cells simultaneously. In the result, the tumor cells will dead **(Figures 1 and 2)**.

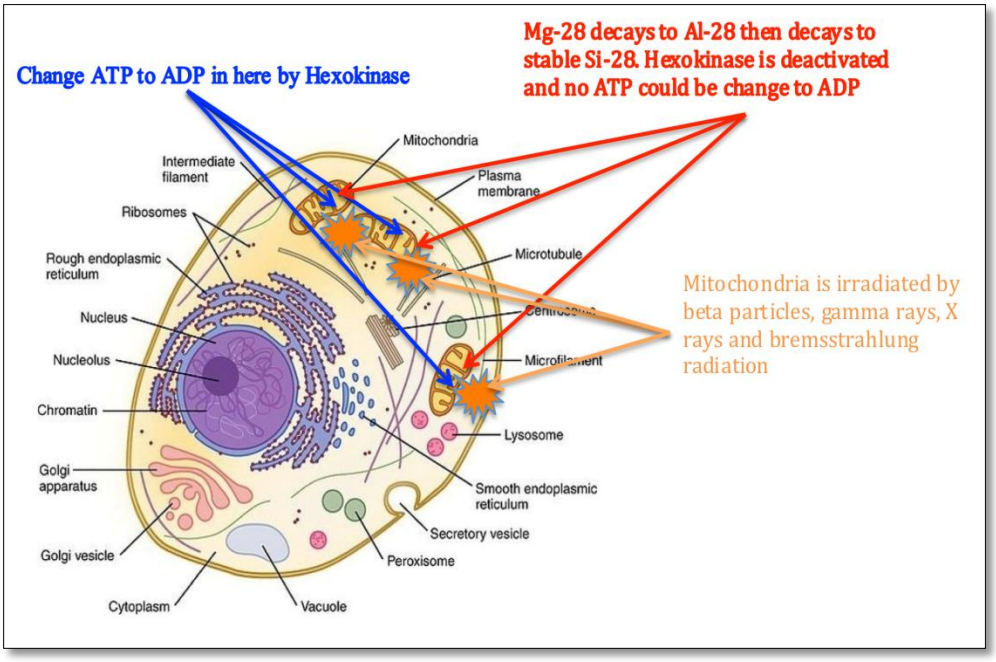

Figure 1. The situation of the cell during deactivation of hexokinase [54].

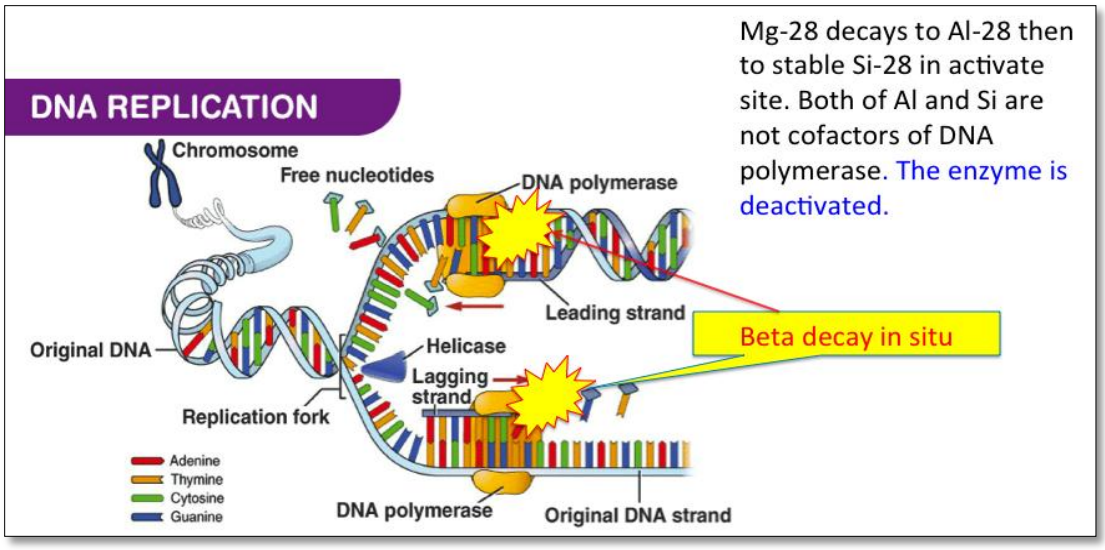

Figure 2. Deactivation of DNA polymerase by ^{28}Mg [55].

CONCLUSION AND RECOMMENDATION

Many authors have studied hexokinase and DNA polymerase [17-32] but no one has used ^{28}Mg to investigate the kinetics, biochemical metabolism and the effect of Mg on the activity of these enzymes. There are studies on ^{28}Mg [53] but only stop at the level of marking and testing the metabolism and endurance of the body with Mg. There are many researches on biochemistry, metabolism and effects of Mg on cancer [34-43] and have revealed some ideas for curing cancer from these studies. Independent studies on hexokinase and DNA polymerase have shown how they work, the catalytic mechanism of these enzymes all recognize the important role of Mg cofactor in converting ATP into ADP and DNA replication.

The study of replacing stable Mg with ^{28}Mg radioactive isotopes in these enzymes for the purpose of deactivating them is a completely new study. It opens up a huge potential for disrupting and controlling important molecular and cellular metabolic processes. If these studies are successful it can be used to treat cancer. Enzymes will be the destination for cofactor radioisotopes [45]. In the ^{28}Mg case, this study will deactivate hexokinase and DNA polymerase and several other enzymes where Mg is the cofactor. This is a breakthrough in inhibiting energy supply for cells and a strong intervention in the process of DNA replication, two processes that determine the existence, development, and replication of cancer cells. Stopping or interrupting these processes in tumors we hope to eradicate this disease. In addition, the radioisotopes are introduced into the nucleus and mitochondria where the enzyme located, the radiation created by them will directly bombard cancer cells with a 100% probability of reaching the target. Free radicals generated by the interaction of radiation with the intracellular environment contribute to the disruption of the molecular level of substrates, proteins, polypeptides and others. All this effect will destroy tumor cells.

The processes of deactivation, irradiation, and reaction with free radicals all occur inside the cell so it can work on all types of cancerous tissue cells and in different stages of cancer. That is, it can destroy various types of cancers and intervene deeply into cancer stages. This is a distinct effect of this method compared to the existing cancer treatments.

Although, there are no evident experimental results we still hope that the proposal perspective is valuable to all of the people who are studying the cancer treatment.

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